ejpmr, 2023,10(4), 44-50

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A RENEWED THREAT IN SYRIA: CHOLERA

Kanaan Al-Tameemi*[1], Raian Alzoaabi[2] and Rana Nassour[3]

[1]Department of Biochemistry and Microbiology, Faculty of Pharmacy, Arab Private University for Science and Technology, Hama, Syria.
[2]Faculty of Dentistry, Arab Private University for Science and Technology, Hama, Syria.
[3]Department of Biology, Faculty of Science, Tishreen University, Latakia, Syria.

***Corresponding Author: Kanaan Al-Tameemi**

Department of Biochemistry and Microbiology, Faculty of Pharmacy, Arab Private University for Science and Technology, Hama, Syria.

Article Received on 02/02/2023 **Article Revised on 23/02/2023** **Article Accepted on 15/03/2023**

ABSTRACT

Cholera is an acute disease caused by small intestine infection with the bacterium *Vibrio cholerae*. *V. cholerae* is a highly motile gram-negative comma-shaped bacterium. It can be transmitted to humans upon ingesting contaminated water and/or food with it. There are hundreds of serogroups of *V. cholerae*, but only two of them can produce cholera toxin, which cause a severe life-threatening cholera disease: O1 and O139. Those two have led to several outbreaks throughout history. Cholera is characterized by acute watery diarrhoea mainly, and may cause severe dehydration, which may end up in serious cases with death in few hours if not treated properly. According to statistics, 92649 suspected were reported in Syria by 15 February 2023, with a 0.11% fatality rate. During the Syrian crisis and the recent devastating earthquake, many facilities have been destroyed. Thus, there is an insistent need to restore the water and sanitation plants and healthcare facilities, and plan awareness raising and vaccination campaigns to efficiently counter the current and future outbreaks. This review focuses on cholera`s history, previous pandemics, current outbreak in Syria, transmission, symptoms, diagnosis methods, treatment and prevention.

KEYWORDS: *V. cholerae*, outbreak, diagnosis, treatment, prevention, Syria.

INTRODUCTION

The term cholera came from the Greek word '*chole'*, which has been used for different gastrointestinal disorders in the past centuries.[1-3] Cholera is an acute infection caused by the bacterium Vibrio cholera[4-6], and it is considered as a global threat to public health highlighting the weak social development. Every year, there are between 1.3 and 4.0 million cases of cholera worldwide, and 21000 to 143000 deaths because of it.[7-9]

THE DISCOVERY OF *V. CHOLERAE*

Cholera was known as acute summer diarrhoea during the 17th century.[1] In the 19th century, there were much deliberation on cholera between European scientists. The arguments focused on two different theories, the miasma theory and the germ theory.[10] Back then, the most acceptable explanation of the epidemics was based on the presumption that they were resulted from a miasma. The miasma was thought to be a deleterious form of "bad air" or a poisonous steam filled with decomposed particles.[10-12] Afterwards, this theory was replaced by the germ theory of disease, based on the assumption that microorganisms can infect the bodies and cause certain illnesses.[10]

John Snow, an English physician, investigated the source of the cholera outbreak in Soho, London in 1854, which is known today as the Broad Street cholera outbreak. At that era, the hygienic conditions of London made the miasma theory entirely acceptable. The sewage system was very bad, and the stink of faeces and rotting garbage was prevalent. Besides, the disease spread more amongst poor people because of their bad hygiene habits and supposed moral corruption. Snow was the first who used modern epidemiological methods to trace the source of the outbreak and understand its real causes. He noticed that the cholera cases were localized around one specific water pump at the southwest corner of the intersection of Cambridge Street and Broad Street. By examining water samples with a microscope, Snow noticed some "white, flocculent particles" in the Broad Street samples.[10] As soon as the pump handle was removed from the Broad Street pump, the cholera spread decreased markedly.[7,10,13] Snow clarified the relationship between cholera outbreak in London and contaminated water.[1,10,12] Yet, he couldn`t identify the microbial agent that cause cholera.[10]

The causative agent responsible for cholera: '*V. cholerae*' was discovered independently by two well-known scientists.[10] The first discovery was in 1854 by

Filippo Pacini, an Italian anatomist.[1,10] However, the scientific community didn`t accept this discovery widely because of the dominated miasmatic theory. The second discovery took place after almost 30 years by Robert Koch, a German bacteriologist, in 1883, which finally favoured the germ theory over the miasmatic theory of disease and made it widespread accepted by everyone.[1,10]

THE HISTORY OF CHOLERA

Cholera led to seven pandemics throughout the 19th and 20th centuries, killing millions of lives, as the following:

- The first pandemic 'Asiatic cholera' (1817 - 1821) started in India and extended to the Far East and other parts of the world.[1]
- The second pandemic (1829-1851) also began in India and extended to China, Europe and America.[1]
- The third pandemic (1852-1860) happened in Russia, and it had a high mortality rate.[1]
- The fourth pandemic (1863-1875) started in the Bengal and reached the Middle East.[1]
- The fifth pandemic (1881-1896) started in India and spread throughout Europe, except for Germany that was hardly affected.[1]
- The sixth pandemic (1899-1923) began in India and spread to the Middle East, northern Africa and Eastern Europe.[1,10] More than 800,000 people passed away in India alone during this pandemic.[1]
- The ongoing seventh pandemic began in Indonesia in 1961 and spread to India, North Africa and Russia.[1] By 1991, cholera had spread across the whole Africa and reached Latin America.[14]

VIBRIOS CLASSIFICATION

Vibrios are gram-negative bacteria that normally occur in saltwater. They have comma-shaped cells, and may connect end to end to form spirals and S shapes.[15] They are extremely motile using a single polar flagellum[15,16], and they seem to vibrate upon moving, hence their name.[13] These bacteria are non-spore forming organisms that may be aerobic or facultative anaerobic.[13,15] Vibrios include many species, such as *V. parahaemolyticus*, *V. mimicus*, *V. hollisae* and *V. cholerae*.[15,17]

V. cholerae is the microbial agent for cholera.[16,18] It usually between 1-3 µm length and 0.5-0.8 µm diameter. Its antigenic structure includes a flagellar H antigen and a somatic O antigen. The pathogenic strains are distinguished from the non-pathogenic ones through distinction their somatic O antigens.[13]

V. cholerae includes hundreds of serogroups, but O1 and O139 can produce cholera toxin, causing the life-threatening cholera disease and leading to outbreaks.[9,18-21]

- *V. cholerae* O139 was identified in Bangladesh in 1992. It caused outbreaks exclusively in Asia in the past, but it has not been identified recently, except for sporadic cases.[21]
- *V. cholerae* O1 is responsible for latest outbreaks.[21] It includes two biotypes: Classical and El Tor, and each of them has unique serotypes: Inaba, Ogawa and rarely Hikojima.[9,13,19,22] Of note, their manifestations are indistinguishable[9,18], although most patients with the El Tor biotype are asymptomatic or develop a mild disease. On the other hand, Classical biotype infections become uncommon lately and are limited to some regions in India and Bangladesh.[9]

As for all other *V. cholerae* serogroups, they are known as "non-cholera *V. cholerae*". They include strains of *V. cholerae* O1 and O139 that do not produce cholera toxin and do not cause epidemics.[20]

TRANSMISSION OF CHOLERA

Cholera is transmitted through ingesting contaminated water and/or food with the bacteria.[6,18,23,24] Humans represent the only natural host for *V. cholerae*, and transmission occur through the faecal-oral route.[6,13,22,24] It is noteworthy that *V. cholerae* may live freely in brackish water and can survive in fresh or saltwater, which interprets the occasional infections by shellfish.[6,22,23]

Today, cholera is almost eradicated in most developed countries.[6,25], but is an endemic in 69 countries in Latin America, Africa and Asia including the Middle East countries.[6,26-28] Lately, cholera is still affecting vulnerable communities, such as Yemen, Iraq and Syria, where sanitation, poor water, hygiene conditions, overcrowding, starvation, natural disasters, refugee displacement, war and conflict increase the risk of infection and outbreaks.[6,13,26,27,29-32]

THE CHOLERA OUTBREAK IN SYRIA IN 2022

Cholera outbreaks were reported in many in African and Asian countries in the past year, including Syria.[33]

The first confirmed case in Syria in 2022 was reported on 22 August for a 9-year-old boy from Aleppo who suffered from acute watery diarrhoea. The infection was confirmed using rapid diagnostic and culture tests.[34]

The Syrian Ministry of Health declared 15 cholera confirmed cases and one death in Aleppo by 10 September 2022.[34,35] Later, acute watery diarrhoea cases spread to other governorates.

By the day of 15 February 2023, 92649 suspected cholera cases that were associated with acute watery diarrhoea from all 14 governorates (Fig. 1). There were 101 reported deaths with a fatality rate of 0.11%.[36] Additionally, *Vibrio cholerae* O1 El-Tor Ogawa was determined as the recent circulating strain in Syria.[37]

Idleb, Aleppo, Deir-ez-Zor and Ar-Raqqa reported most of the cases, with 30%, 23.9%, 22.3% and 19% of total cases, respectively.[36,38] Nonetheless, all Syrian

governorates are on the line, owing to the severe water crisis and the considerable number of internally displaced population.[38]

Many facilities were damaged after more than a decade of Syrian conflict, as one sixth of wells, one quarter of sewage treatment plants, one third of water towers, two thirds of water treatment facilities and half of pumping stations were destroyed.[38]

Moreover, the destructive earthquake in 6 February 2023 had a serious impact on the cholera response actions. The earthquake negatively affected easy access to medical services, decreased partner capability and reduced the already limited funds on hand, not to mention the negative impact on the workforce`s mental health. Until 15 February 2023, 171 health facilities were damaged and 15 ones had to temporarily suspend their medical operations.[36]

After the devastating earthquake, thousands of people are staying in crowded shelters, and many of them don`t have suitable access to safe water and sanitation. Thus, the risk of increasing waterborne infections like Cholera is extremely high.[36] Hence, it is compelling to establish emergency plans to cease the current outbreak and long-term investment to restore the water and sanitation systems to prohibit future outbreaks.[38]

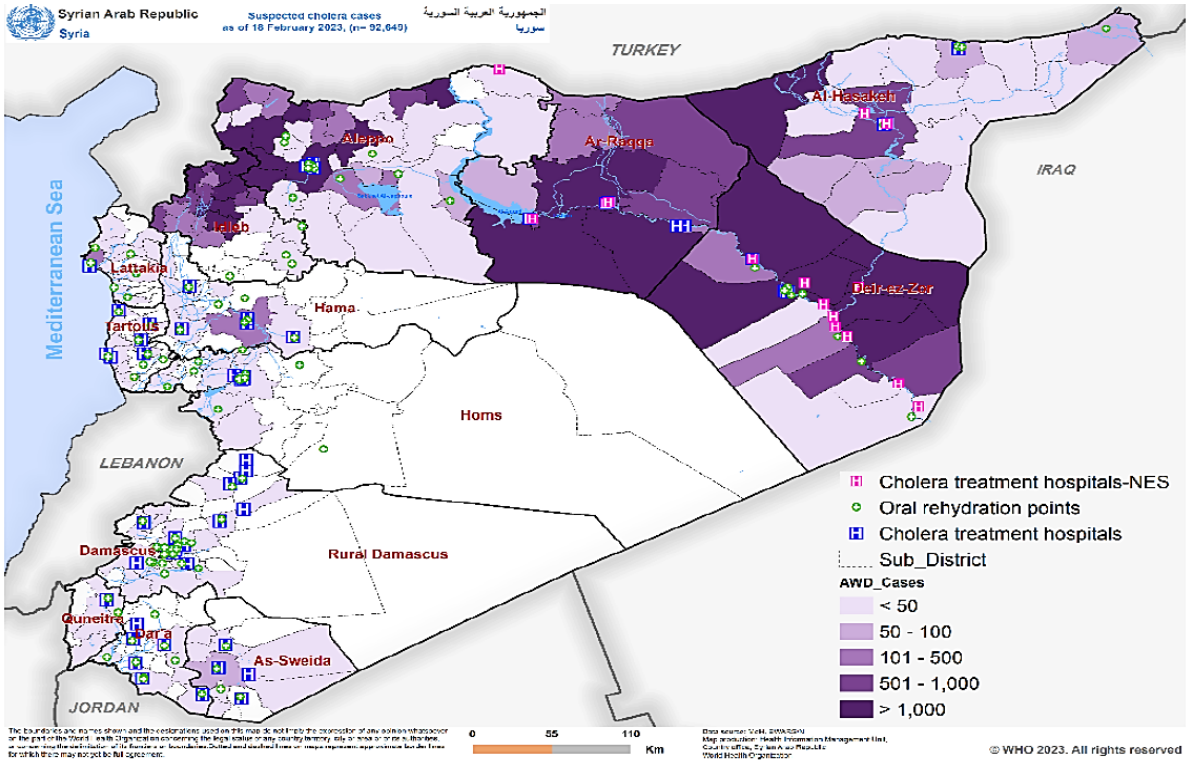

Fig. 1: Distribution of suspected cholera cases in Syria until 18 February 2023.[36]

SYMPTOMS

Cholera is a very virulent disease. It takes from 12 hours to 5 days to show symptoms after consuming contaminated water or food with *V. cholerae*.[8,21] Cholera affects all age-groups from children to adults.[8,21,30] Most infected individuals are asymptomatic, yet the bacteria can be found in their faeces for 1-10 days after infection, which means that they can return to the environment, and infect healthy people.[8,21] As for the symptomatic patients, most of them develop mild or moderate symptoms.[8,21], while few of them (about 1 in 10 people) develop severe symptoms that include the following in the early stages:

- Profuse watery diarrhoea (rice-water stools).[3,15,39,40]
- Thirst.[23,26,31,39]
- Nausea and vomiting.[5,25,26,39,40]
- Irritability and restlessness.[23,39]
- Muscle cramps as a result of salts loss.[4,23,26,39,40]

Physicians should check dehydration signs when examining a patient with profuse watery diarrhoea, which include:

- Mucous membranes dryness.[26,39]
- Skin elasticity depletion.[26,39]
- Low blood pressure.[26,31,39]
- Rapid heart rate.[26,39]

Patients with severe cholera can experience severe dehydration, which may lead to kidney failure, and end up with shock, coma and death within few hours, if left untreated.[15,23,39]

Some patients are more likely to suffer from acute disease and poor outcomes. They include people with achlorhydria, blood type O, chronic medical conditions, and individuals who don't have easy access to medical services.[6,9,40]

DIAGNOSIS

It is not possible to confirm a cholera infection depending on clinical symptoms only. Thus, the ideal method is to isolate and identify *V. cholerae* serogroup by culturing a stool sample.[18,19,22,31,40,41,42]

Cary Blair media is perfect for transport, and the selective thiosulfate–citrate–bile salts agar (TCBS) is the best for isolation and identification.[41] As for regions with limited or no laboratory tests, the Crystal® VC dipstick rapid test can be useful.[18,41,43] Of note, the sensitivity and specificity of this test is not ideal.[41,44] Hence, it is recommended to test the positive faecal sample by the later test with the traditional culture-based methods suitable for the isolation and identification of *V. cholerae*.[41]

TREATMENT

Cholera is a readily treatable disease through rehydration therapy. Antibiotics and zinc supplements could be useful in certain cases.[21,45,46,47]

Rehydration therapy: Dehydration can be deadly if not treated appropriately. Rehydration can save the lives of more than 99% of cholera patients.[24,45,48] Otherwise, at least 1 in 4 to nearly half of patients may lose their lives.[45]

Rehydration therapy include

- Sufficient volumes of an oral rehydration salts solutions.[21,40,45]
- Intravenous (IV) fluids.[40,45]
- Electrolytes.[45]

Antibiotic treatment: Concurrently with the rehydration treatment, antibiotic treatment is recommended for:

- Seriously sick patients.[21,40,46]
- Patients with severe dehydration or a little dehydration, as long as they continue to lose a vast volume of stool during rehydration.[21,46]
- Pregnant women.[46]
- Patients with comorbidities such as HIV and severe acute malnutrition.[46]

Antibiotics are given once the patient can endure oral medication. Doxycycline is considered as a first-line treatment for children and adults, including pregnant women. Ciprofloxacin and azithromycin are alternatives in the case of doxycycline resistance.[46]

Zinc treatment: Previous study revealed that zinc supplementation reduced the duration and intensity of diarrhoea in cholera paediatric patients.[21,40,47] Thus, it is recommended to take 20 mg zinc per day for children older than six months.[47] Of note, Antibiotics should be taken 2 hours before or 4-6 hours after zinc to avoid the reduction of certain antibiotics absorption (like ciprofloxacin).[47] Cholera patients usually recover without long-term consequences, when they are treated quickly. Besides, recovered patients do not normally become carriers of the bacteria, and they may fall ill when exposing to the bacteria once more.[39]

Prevention and control

To prevent cholera from spreading, combined strategies are used:

Surveillance: Cholera incidences are detected based on clinical suspicion in patients who have severe watery diarrhoea. Then this suspicion is confirmed using laboratories diagnosis. The capacity to detect and monitor cholera incidences is crucial for a successful surveillance system and to plan control strategies.[21,49,50,51,52]

Water and sanitation interventions: The sustainable solution for controlling cholera lies in economic development and easy access to clean drinking water and suitable sanitation.[8,21,25,53,54,55,56,57]

Community engagement: This means that people and communities are part of the development process and awareness programs.[21,58] Local culture practices are essential to promote precaution actions like the adoption of:

- Protective hygiene procedures like hand washing with soap.[21,25,39,53,55]
- Eat well cooked food.[21,40]
- Eat peelable fruits and vegetables.[26,31,40]
- Avoid raw or undercooked seafood.[3,26,40]
- Avoid street vendors`s drinks or food.[25,40]
- Safe disposal of human faeces from cholera patients to avoid contamination.[21,39]
- Funeral practices for patients who passed away from cholera to avoid infection amongst attendees.[21,56]

Vaccines: There are three world health organization (WHO) pre-qualified oral cholera vaccines; Dukoral®, Euvichol-Plus® and Shanchol™. All of them require two doses for full protection.[21,59]

Dukoral is permitted to all ages older than 2 years old. The time interval between the doses must be 1 to 6 weeks. Children between two and five years usually need a third dose. Dukoral® is principally used for travellers. Two doses of Dukoral® protect from cholera for two years.[21,60]

On the other hand, Euvichol-Plus® and Shanchol™ are permitted for all ages older than one year. There must be at least 15 days delay between the two doses of these vaccines. Two doses of Shanchol™ and Euvichol-Plus® provide protection against cholera for three years at a minimum.[21,60]

Of note, the recent unprecedented rise in cholera outbreaks has obligated the International Coordinating Group (ICG) to temporarily use a single-dose regime instead of the standard two-dose vaccination. This strategy will allow vaccine providing in more countries.

The one-dose approach has proven to be effective during outbreaks, even though the exact duration of protection is still under investigation, with noticeable much lower protection among children.[32]

The vaccination campaign began in Syria on 4 December 2022 in some governorates like Ar Raqqa, Deir ez-Zoir and Aleppo. The aim was to vaccinate 2 million people via 63 stations and 685 mobile squads. By 18 December 2022, 577000 people took the vaccines.[36]

CONCLUSION

Cholera is an intestinal disease caused by an infection with the bacterium *V. cholerae*. It is an ancient disease, and it had caused seven pandemics since the early 19th century and killed millions of lives around the world. It can be transmitted to humans through contaminated water and/or food with the bacterium. The best method for diagnosis is culture a stool sample on a selective thiosulfate–citrate–bile salts agar (TCBS).

All Syrian governorates reported cholera cases in the period between 22 August 2022 and 15 February 2023. This could be due partially to the water and sanitation facilities damage during the Syrian conflict and healthcare facilities impairment in the devastating earthquake of 6 February 2023. Combined strategies should be used for cholera prevention, including the surveillance, improving water and sanitation facilities, repairing healthcare centres, hygiene measures and oral vaccines.

Author contributions: All authors contributed equally in the design and writing of the manuscript.

Conflicts of Interest: None.

REFERENCES

1. Azizi MH, Azizi F. History of Cholera Outbreaks in Iran during the 19th and 20th Centuries. MEJDD, 2010; 2(1): 51-5.
2. Kousoulis AA. Etymology of Cholera. Emerg Infect Dis., 2012; 18(3): 540.
3. Cholera. Available from: https://klmhealthservices.com/en/travel-preparation/diseases/cholera/. [Accessed on 2022 Oct 8].
4. Kraft S. Everything you need to know about cholera. [Cited 2018 Jan 11]. Available from: https://www.medicalnewstoday.com/articles/189269. [Accessed 2022 Nov 16].
5. Grognot M, Mittal A, Mah'moud M, Taute KM. *Vibrio cholerae* motility in aquatic and mucus-mimicking environments. Appl Environ Microbiol., 2021; 87(20): e01293-21. DOI: 10.1128/AEM.01293-21.
6. Rodriguez JAO, Kahwaji CI. *Vibrio Cholerae* [Updated 2022 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526099/. [Accessed 2022 Oct 9].
7. Jensen PKM, Grant SL, Perner ML, Hossain ZZ, Ferdous J, Sultana R, Almeida S, Phelps M, Begum A. Historical and contemporary views on cholera transmission: are we repeating past discussions? Can lessons learned from cholera be applied to COVID-19?. APMIS, 2021; 129(7): 421–430. DOI: 10.1111/apm.13102.
8. World health organization: Cholera. Available from: https://www.who.int/health-topics/cholera#tab=tab_1. [Accessed on 2022 Oct 4].
9. Centers for Disease Control and Prevention. Sources of Infection & Risk Factors. Available from: https://www.cdc.gov/cholera/infection-sources.html. [Last reviewed on 13 April 2022, accessed 2022 Oct 6].
10. Lippi D, Gotuzzo E, Caini S. Cholera. Microbiol Spectr., 2016; 4(4):PoH-0012-2015. DOI:10.1128/microbiolspec.PoH -0012-2015.
11. Karamanou M, Panayiotakopoulos G, Tsoucalas G, Kousoulis AA, Androuts G. From miasmas to germs: A historical approach to theories of infectious disease transmission. Le Infezioni in Medicina, 2012; 1: 52-6.
12. Kannadan A. History of the Miasma Theory of Disease. ESSAI, 2018; 16: Article 18. DOI: https://dc.cod.edu/essai/vol16/iss1/18.
13. Handa S. Cholera. *Medscape* 2021 Feb 3. Available from: https://emedicine.medscape.com/article/962643-overview. [Accessed 2022 Oct 8].
14. Gavi- Vaccine work: Cholera's 7th Pandemic turns 60. 2021 December 23. Available from: https://www.gavi.org/vaccineswork/choleras-7th-pandemic-turns-60?gclid=Cj0KCQjw1vSZBhDuARIsAKZlijQyZIXehM4bohLiTPJqMeUnYOc67YWl7EEJrqNXOTBNDNVArpBA3XkaAnIaEALw_wcB. [Accessed 2022 Oct 5].
15. Ryan KJ, Ahmed N, Alspaugh JA, Drew WL, Pottinger P, Reller LB, Reller ME, Steinbrink JM, Sterling CR, Vedantam G, Weiessman S. Sherris & Ryan's Medical Microbiology. 8th edition. USA: McGraw Hill; 2022. Chapter number 32, Vibrio, Campylobacter, and Helicobacter; p. 1162-88.
16. Fernandeza NL, Hsueha BY, Nhua NTQ, Franklina JL, Dufoura YS, Waters CM. *Vibrio cholerae* adapts to sessile and motile lifestyles by cyclic di-GMP regulation of cell shape. PNAS, 2020; 117(46): 29046-54.
17. Bush LM, Vazquez-Pertejo MT. Noncholera *Vibrio* Infection. MSD Manuals. Reviewed on 2022 April Available from: https://www.msdmanuals.com/professional/infectious-diseases/gram-negative-bacilli/noncholera-vibrio-infections. Last modified on 2022 Sep 2022. [Accessed 2022 Oct 8].

18. LaRocque R, Harris JB. Cholera: Clinical features, diagnosis, treatment, and prevention. *UpToDate*. [Reviewed 2022 Sep.]. Available from: https://www.uptodate.com/contents/cholera-clinical-features-diagnosis-treatment-and-prevention. [Last updated 2022 Oct 11, accessed 2022 Oct 26].
19. Mandal A. Cholera Diagnosis. News-medical. [Cited 2019 Feb 26]. Available from: https://www.news-medical.net/health/Cholera-Diagnosis.aspx. [Accessed 2022 Oct 8].
20. Centers for Disease Control and Prevention. Non-cholera *Vibrio cholerae* Infections. [Reviewed 2020 Sep 2]. Available from: https://www.cdc.gov/cholera/non-01-0139-infections.html. [Accessed 2022 Oct 6].
21. World health organization. Cholera. [Cited 2022 Mar 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/cholera?gclid=CjwKCAjws--ZBhAXEiwAv-RNL0p1Ic_aigaqTXmx-yGHWQ3XCaa618dxlJatBA44ErQA0PVxuGX49RoC7JQQAvD_BwE. [Accessed 2022 Oct 5].
22. Alberta Public Health Disease Management Guidelines. Cholera (O1 andO139). Government of Alberta: Alberta Health 2021; 12 pages.
23. Cleveland Clinic. Cholera. [Reviewed 2021 Apr 30]. Available from: https://my.clevelandclinic.org/health/diseases/16636-cholera. [Accessed 2022 Oct 8].
24. European Centre for Disease Prevention and Control. Cholera. Available from: https://www.ecdc.europa.eu/en/cholera. [Accessed 2022 Oct 7].
25. Mandal A. Cholera Transmission, Spread, Prevention & Treatment. News-medical. [Cited 2019 May 13]. Available from: https://www.news-medical.net/health/Cholera-Transmission-Spread-Prevention-Treatment.aspx. [Accessed 2022 Oct 8].
26. Dunkin MA. Cholera. WebMD. [Cited 2021 Jul 25]. Available from: https://www.webmd.com/a-to-z-guides/cholera-faq. [Accessed 2022 Oct 9].
27. Lessler J, Moore SM, Luquero FJ, McKay HS, Grais R, Henkens M, Mengel M, Dunoyer J, M'bangombe M, Lee EC, Djingarey MH, Sudre B, Bompangue D, Fraser RSM, Abubakar A, Perea W, Legros D, Azman AS. Mapping the burden of cholera in sub-Saharan Africa and implications for control: an analysis of data across geographical scales. Lancet, 2018; 391: 1908–15.
28. Mandal A. Cholera Epidemiology. News-medical. [Cited 2019 Feb 26]. Available from: https://www.news-medical.net/health/Cholera-Epidemiology.aspx. [Accessed 2022 Oct 8].
29. Zarocostas J. Cholera outbreak in Haiti-from 2010 to today. Lancet, 2017; 389(10086): 2274-5. DOI: 10.1016/S0140-6736(17)31581-7.
30. Global Task Force on Cholera Control. Cholera. Available from: https://choleraoutbreak.org/book-page/cholera. [Accessed 2022 Oct 8].
31. Normandin B. Cholera. Healthline. [Cited 2022 Jan 31]. Available from: https://www.healthline.com/health/cholera. [Accessed 2022 Oct 8].
32. World health organization: Shortage of cholera vaccines leads to temporary suspension of two-dose strategy, as cases rise worldwide. Available from: https://www.who.int/news/item/19-10-2022-shortage-of-cholera-vaccines-leads-to-temporary-suspension-of-two-dose-strategy--as-cases-rise-worldwide. [Cited 2022 Oct 19, accessed 2022 Nov 16].
33. European Centre for Disease Prevention and Control: Cholera worldwide overview. Updated on 2022 Sep 21. Available from: https://www.ecdc.europa.eu/en/all-topics-z/cholera/surveillance-and-disease-data/cholera-monthly. [Accessed 2022 Oct 26].
34. World health organization. Syrian Arab Republic: WHO Syria Situation Report #6 Cholera Outbreak. [Published 2022 Sep 27]. Available from: https://reliefweb.int/report/syrian-arab-republic/syrian-arab-republic-who-syria-situation-report-6-cholera-outbreak-27-september-2022.
35. United Nations. United Nations Resident and Humanitarian Coordinator in Syria, Imran Riza, statement on the outbreak of cholera in Syria, Damascus. [Published 2022 Sep 12]. Available from: https://reliefweb.int/report/syrian-arab-republic/united-nations-resident-and-humanitarian-coordinator-syria-imran-riza-statement-outbreak-cholera-syria-12-september-2022-enar.
36. OCHA and World health organization. Whole of Syria Cholera Outbreak Situation Report no. 13. [Published February 28, 2023]. Available from: https://reliefweb.int/report/syrian-arab-republic/whole-syria-cholera-outbreak-situation-report-no-13-issued-28-february-2023 .
37. United Nations. Cholera spreading throughout Lebanon, WHO warns. [Published on 2022 Nov 1]. Available from: https://news.un.org/en/story/2022/11/1130067.
38. UNICEF. Syria Cholera Response Situation Report for 04 October 2022. [Published 2022 Oct 4]. Available from: https://reliefweb.int/report/syrian-arab-republic/unicef-syria-cholera-response-situation-report-04-october-2022.
39. Centers for Disease Control and Prevention. Illness and Symptoms. [Reviewed 2020 Oct 2]. Available from: https://www.cdc.gov/cholera/illness.html. [Accessed 2022 Oct 6].
40. Mayo Clinic. Cholera. [Cited 2022 Feb 26]. Available from: https://www.mayoclinic.org/diseases-conditions/cholera/symptoms-causes/syc-20355287. [Accessed 2022 Oct 6].
41. Centers for Disease Control and Prevention. Diagnosis and Detection. [Reviewed 2022 June 6]. Available from:

https://www.cdc.gov/cholera/diagnosis.html. [Accessed 2022 Oct 6].
42. Chowdhury G, Senapati T, Das B, Kamath A, Pal D, Bose P, Deb A, Paul S, Mukhopadhyay AK, Shanta Dutta S, Ramamurthy T. Laboratory evaluation of the rapid diagnostic tests for the detection of *Vibrio cholerae* O1 using diarrheal samples. PLoS Negl Trop Dis., 2021; 15(6): e0009521. DOI: 10.1371/journal.pntd.0009521.
43. Falconer J, Diaconu K, O'May F, Gummaraju A, Victor-Uadiale I, Matragrano J, Njanpop-Lafourcade BM, Ager A. Ager A. Cholera diagnosis in human stool and detection in water: A systematic review and meta-analysis. PLOS ONE, 2022; 17(7): e0270860. DOI: 10.1371/journal.pone.0270860.
44. Muzembo BA, Kitahara K, Ohno A, Debnath A, Okamoto K, Miyoshi SI. Cholera Rapid Diagnostic Tests for the Detection of *Vibrio cholerae* O1: An Updated Meta-Analysis. Diagnostics, 2021; 11: Article 2095. DOI: 10.3390/diagnostics11112095.
45. Centers for Disease Control and Prevention. Rehydration Therapy. [Reviewed 2020 Oct 2]. Available from: https://www.cdc.gov/cholera/treatment/rehydration-therapy.html. [Accessed 2022 Oct 6].
46. Centers for Disease Control and Prevention. Antibiotic Treatment. [Reviewed 2022 June 1]. Available from: https://www.cdc.gov/cholera/treatment/antibiotic-treatment.html. [Accessed 2022 Oct 6].
47. Centers for Disease Control and Prevention. Zinc Treatment. [Reviewed 2020 Oct 2]. Available from: https://www.cdc.gov/cholera/treatment/zinc-treatment.html. [Accessed 2022 Oct 6].
48. Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. Lancet, 2017; 390(10101): 1539-49. DOI: 10.1016/S0140-6736(17)30559-7.
49. Global Task Force on Cholera Control (GTFCC). Surveillance Working Group. Interim Guidance Document on Cholera Surveillance 2017. 31 pages.
50. Azman AS, Moore SM, Lessler J. Surveillance and the global fight against cholera: Setting priorities and tracking progress. Vaccine, 2020; 38(Supplement 1): A28-30.
51. Ganesan D, Gupta SS, Legros D. Cholera surveillance and estimation of burden of cholera. Vaccine, 2020; 38(Supplement 1): A13-7.
52. Hegde ST, Lee EC, Khan AI, Lauer SA, Islam MT, Bhuiyan TR, Lessler J, Azman AS, Qadri F, Gurley ES. Clinical Cholera Surveillance Sensitivity in Bangladesh and Implications for Large-Scale Disease Control. JID, 2021; 224(S7): S725–31. DOI: 10.1093/infdis/jiab418.
53. Yates T, Allen J, Leandre Joseph M, Lantagne D. WASH interventions in disease outbreak response. Humanitarian Evidence Programme. Oxford: Oxfam GB; 2017. 88 pages.
54. UNICEF. Sub-strategy on WASH interventions related to cholera prevention and response [EN/PT]. [Published 2019 Apr 6]. Available from: https://reliefweb.int/report/mozambique/sub-strategy-wash-interventions-related-cholera-prevention-and-response-enpt.
55. Alassar MM, Adegboye OA, Emeto TI, Rahman KM, Mashood LO, Elfaki FAM. Severe dehydration among cholera patients in Yemen: A cohort profile. GERMS, 2020; 10(4): 338-45.
56. D'Mello-Guyett L, Gallandat K, Bergh RV, Taylor D, Bulit G, Legros D, Maes P, Checchi F, Cumming O. Prevention and control of cholera with household and community water, sanitation and hygiene (WASH) interventions: A scoping review of current international guidelines. PLOS ONE, 2020; 15(1):e0226549. DOI: 10.1371/journal.pone.0226549.
57. Eurien D, Mirembe BB, Musewa A, Kisaakye E, Kwesiga B, Ogole F, Ayen DO, Kadobera D, Bulage L, Ario AR, Zhu BP. Cholera outbreak caused by drinking unprotected well water contaminated with faeces from an open storm water drainage: Kampala City, Uganda, January 2019. BMC Infectious Diseases, 2021; 21: Article 1281. DOI: 10.1186/s12879-021-07011-9.
58. Nayyara A, Privor-Dumm L. Cholera control and prevention: Role of evidence-based advocacy and communications. Vaccine, 2020; 38(Supplement 1): A178-80.
59. Holmgren J. Modern History of Cholera Vaccines and the Pivotal Role of icddr,b. JID, 2021; 224(Supplement 7): S742–8.
60. Centers for Disease Control and Prevention. Vaccines. [Reviewed 2022 Sep 30]. Available from: https://www.cdc.gov/cholera/vaccines.html. [Accessed 2022 Oct 6].